2018 National STD Prevention Conference

Missed Opportunities for PrEP Prescribing in High-Risk Populations

When patients adhere to pre-exposure prophylaxis (PrEP) regimens, it can reduce the risk of HIV infection by up to 92%.1

PrEP is recommended for individuals who are at a higher risk for HIV, including men who have sex with men (MSM) and individuals who use drugs. However, a new survey conducted by investigators from the San Francisco Department of Public Health suggests that less than half of all health care providers had ever prescribed PrEP.2

“[This brief questionnaire] was key in evaluating how providers assess sexual risk for HIV and sexually transmitted diseases and their PrEP (continuing on page 20)

CDC Reports Sharp, Continuous Increase in STDs Over Past 4 Years

A new analysis released by the US Centers for Disease Control and Prevention (CDC) reveals a steep and continuous increase in the number of sexually transmitted diseases (STDs) over the past 4 years.3

Specifically, more than 2.3 million cases of chlamydia, gonorrhea, and syphilis were diagnosed in 2017 in the United States, an increase of about 200,000 cases since 2016 and 31% more than in 2013. The 2017 data marks the fourth consecutive year in which sharp increases in STD incidence have been reported.

A 76% increase in the number of primary and secondary cases of syphilis was reported in the analysis, from 17,375 cases in 2013 to 30,644 cases in 2017. The majority of these cases (70%) occurred among those (continuing on page 20)

EMERGING & RE-EMERGING DISEASES

Zika: Where Are We Now?

By Laurie Saloman, MS

The Zika virus, which dominated mainstream headlines in 2016 with reports of infected women giving birth to babies with defects, has receded into the background. With the virus and its complications no longer front-page news, people might be forgiven for assuming the threat of this mosquito-borne plague no longer exists. But experts say Zika, which is transmitted by the Aedes aegypti mosquito, still presents a clear and present danger to travelers and residents in certain parts of the world, (continuing on page 20)

AIDS 2018

Using a “Kick-and-Kill” Approach to Cure HIV

Initial results from the first randomized clinical trial dedicated to evaluating an experimental “kick-and-kill” approach to eradicating dormant HIV hiding in the body were reported by investigators at the International AIDS Society’s annual meeting.

Although the trial, referred to as the RIVER study, did not yield a difference in effect between those who received the kick-and-kill therapy and those who were given standard antiretroviral treatment (ART), the investigators stressed that the kick-and-kill approach opens the door to exploring (continuing on page 21)

IAS–USA Releases 2018 Guidelines for HIV Treatment and Prevention

The International Antiviral Society–USA (IAS–USA) has issued new guidelines for the prevention and treatment of HIV infection in adults, an update to guidelines released in 2016. The updated guidelines are based on new research findings, drugs, approaches, and data that focus on adults 18 years or older who are infected with HIV or at risk of becoming infected.

A focus on the antiretroviral therapy (ART) as the cornerstone of HIV prevention and treatment, remains in the 2018 update, while (continuing on page 21)

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Plazomicin: A Novel Aminoglycoside

By Maria Heaney, PharmD, and Jason Gallagher, PharmD, FCCP, FIDSA, BCPS

(continued on page 6)

Patients With Diabetes Soon to Have New Option for ABSSSIs

Patients with diabetes who were treated for acute bacterial skin and skin structure infections (ABSSSIs) by iclaprim (Motif Bio) had fewer adverse events (AEs) than patients with diabetes who were treated with vancomycin, according to the results of a recent study. “[Patients with diabetes] are running out of many options when it comes to antibiotics treating ABSSSIs,” corresponding author David B. Huang, MD, PhD, chief medical officer at Motif Bio, shared in an interview with Contagion®. “The reasons the options are limited in this population and why there are poor outcomes among [patients with (continued on page 22)
Questions related to editorial content and submissions should be sent to Associate Editorial Director Danielle Mroz, MA: DMroz@ContagionLive.com.
When I teach infectious diseases (ID) to students in multiple health professions, I like to highlight how they are like a puzzle: Knowledge of the organisms that cause infections combined with knowledge of the pharmacology and spectrum of activity of antimicrobial agents leads to rational antibiotic choices. This is one of the areas of ID that I find most appealing because I am often in the scenario of having to choose agents for resistant infections based on in vitro data, pharmacokinetic/pharmacodynamic studies, logic—and if I’m lucky—some retrospective studies. Although clinically interesting, this situation is not ideal. It is borne out of necessity, as resistant infections are difficult to study in controlled trials, and the epidemiology of antimicrobial resistance is constantly changing.

This issue of Contagion® will print shortly after the publication of a long-awaited clinical trial that was 5 years in the making. The MERINO trial tested the hypothesis that a β-lactamase inhibitor combination is noninferior to a carbapenem for the treatment of bacteremia caused by Enterobacteriaceae resistant to third-generation cephalosporins.1 Previous retrospective studies examining the issue have had mixed results, and many clinicians have differing opinions. After screening over 1600 patients to find 391 to enroll, the investigators have an answer: Piperacillin/tazobactam use was associated with higher mortality than meropenem.

This is a result that few in ID wanted to see because it can be used to justify (often correctly) more use of carbapenems, which in turn can lead to selection pressure encouraging the growth of carbapenem-resistant organisms. However, unpopularity does not lead to invalidity. The single-best-designed study examining empiric regimens for presumed extended-spectrum β-lactamase–producing bloodstream infections has concluded that carbapenems save lives.

ID practitioners were not the only group to receive an evidence-based wake-up call recently. The long-standing practice of using aspirin for primary prevention of cardiovascular events is being reevaluated after several recently published studies. More data in ID pharmacotherapy is emerging that reevaluates the need for intravenous therapy for several disease states, including endocarditis and osteomyelitis. As these and other prospective studies are reported, it is up to all of us in health care to evaluate the level of evidence in our own practices and continue to evolve, just like the organisms we work to treat.
Zika: Where Are We Now?

The virus may be fading from mainstream headlines, but it is active and physicians must stay vigilant.

BY LAURIE SALOMAN, MS

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The drug presents a new option for patients at high risk of infections caused by organisms such as carbapenem-resistant Enterobacteriaceae.

BY MARIA HEANEY, PHARMD*, AND JASON GALLAGHER, PHARMD, FCCP, FIDSA, BCPS*

10 Improving Antimicrobial Stewardship in the Management of Respiratory Infections

As knowledge and awareness of antimicrobial resistance increase, clinicians must continue to adopt strategies for improving antibiotic use.

BY NICOLA M. PARRY, BVSC, MRCVS, MSC, DACVP, ELS

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BY AMY C. MIN, PHARMD, BCACP, AAHIVP*

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Stewards from high-income countries must assist low- to middle-income countries in antibiotic stewardship.

BY DEBRA GOFF, PHARM.D, FCCP*, ANGELIKI MESSINA, MS, PHARM., BS, PHARM.*, AND EMILY HEIL, PHARMD, BCPS-AQ ID*


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BY NIHAAL KARNIK, MD; JAMES ROSSI, MD; ROHAN PARIKH, MD; AND RAVINDRA SANGITHA, MD

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Alleged Penicillin Allergies Lead to Higher Risk of MRSA and *C. difficile*

By Tiffany Lee, PharmD

Penicillins are among the most commonly reported medications with the potential to trigger an allergic reaction; however, many patients with a documented penicillin allergy do not have a true immunoglobulin E (IgE)-mediated reaction or have outgrown a childhood allergy. These allergy labels translate to important clinical implications, as β-lactams are often the antibiotics of choice for many infections. In addition to compromising clinical outcomes, the use of alternative antibiotics has been shown to increase rates of drug toxicity, hospital lengths of stay, readmission rates, and associated health care costs. Alternative agents are often broader spectrum, subjecting patients to collateral damage and subsequent selection for resistant organisms and *Clostridium difficile*.

Using national electronic medical data from the United Kingdom, investigators on a retrospective study sought to associate the risks of acquiring methicillin-resistant *Staphylococcus aureus* (MRSA) or *C. difficile* in patients with documented penicillin allergies. Patients with and without a penicillin allergy were matched based on age, sex, and study entry time. Those with a history of MRSA or *C. difficile* infection were excluded.

A total of 64,141 patients with a declared penicillin allergy were included and compared with 237,258 patients without a documented allergy. Overall, there was a small predominance in women with a median age of about 57 years. Cohort characteristics were well balanced between the 2 study arms.

For the patients with a documented penicillin allergy, most reactions were thought to be secondary to a true allergy (74.5%) versus drug intolerance (14.5%) or an adverse effect (11.1%). Investigators considered many of these reactions to be of moderate severity (86%) and of likely certainty (73.6%).

During a 6-year follow-up period, there were increased rates of MRSA (0.689% vs 0.389%) and *C. difficile* (0.689% vs 0.323%) in patients with a penicillin allergy compared with those without. Adjusted hazard ratios for patients with a penicillin allergy were 1.69 and 1.26 for acquiring MRSA and *C. difficile*, respectively. Unsurprisingly, this population had a higher use of β-lactam alternatives including macrolides, clindamycin, and fluoroquinolones. The authors concluded that patients with a listed penicillin allergy are at a significantly higher risk for MRSA and *C. difficile*, in part as a result of the use of alternative antibiotics.

Findings from this study add further credence to concerns about the collateral damage inappropriately labeled penicillin allergies can cause. Although prior studies evaluating the impact of penicillin allergies have focused on patient-centered outcomes, this study also compounded its findings with public health and infection control implications. It is imperative, therefore, that antimicrobial stewardship programs continue to spearhead initiatives to elucidate and appropriately delabel penicillin allergies, and provide ongoing education regarding the risks of alternative antibiotics. ▲

References available at ContagionLive.com.

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Early Adjunctive Corticosteroids Do Not Improve Outcomes in HIV-Negative Adults With PcP

By Liza Vaezi, PharmD, MSc, BCPS-AQID

The clinical characteristics and outcomes of Pneumocystis jirovecii pneumonia (PcP) differ in immunocompromised patients with and without HIV. Although evidence suggests improved survival with early adjunctive corticosteroids in patients with HIV and PcP, limited data for HIV-negative patients with PcP suggest adjunctive corticosteroids might not improve outcomes.

Wieruszewski et al evaluated the impact of early corticosteroids as an adjunct to anti-PcP therapy in acutely ill immunocompromised adults without HIV. Outcomes of patients who received early corticosteroid therapy (within 48 hours of PcP diagnosis or therapy) were compared with those who did not.

Among the 323 patients in the study (early steroids, *n* = 258; nonearly steroids, *n* = 65) the median age was 65 years; 63% were male; 92% were white; 97% had immunosuppressive disease (hematologic malignancy 50%), and 60% had a history of immunosuppressive therapy prior to hospitalization. Patients received appropriate anti-PcP therapy (primarily sulfamethoxazole/trimethoprim) and a median dose of prednisone 60 mg daily.

Severity adjusted (for baseline hypoxemia) regression and propensity-matched analyses found that administration of steroids was associated with less improvement in the early group than the nonearly group at day 5, with a mean ΔSOFA score difference of –0.47 (95% CI, –0.73 to –0.21; *P* = .001) and –0.46 (95% CI, –0.84 to –0.08; *P* = .017), respectively. No differences were observed in the odds of having at least 1 point improvement in SOFA score, at day 5 compared with baseline between groups (adjusted OR, 0.76 [95% CI, 0.24–2.28]; *P* = .61) (see Table online). No differences in mortality, length of stay, admission to the ICU, or need for mechanical ventilation were found between early and nonearly steroid recipients.

This is the largest study to date on HIV-negative patients with PcP. Although this study was nonblinded, nonrandomized, and retrospective, the use of multivariable adjustments and propensity-matched cohort analyses confirmed the results of previous studies that found no observable benefit of early steroids in patients with PcP who are HIV-negative. The authors speculated that differences in patients with PcP who are HIV-negative versus those who are positive “may be due to a reduced response among those with earlier exposure to corticosteroids immediately preceding PcP presentation.”

Clinicians should reevaluate routine adjunctive steroid therapy for patients with PcP who are HIV-negative in the absence of other compelling indications for receiving steroids. Robust randomized prospective studies are warranted to further explain the pathophysiological differences in immune status that predispose patients who are HIV negative to intensified inflammatory response to PcP antimicrobial therapy and their ability to respond to anti-inflammatory agents. ▲

References available at ContagionLive.com.
Chagas Disease Drug Now Commercially Available
By Einav Keet

A new report from investigators at the US Centers for Disease Control and Prevention (CDC) details the investigational use of a drug, benznidazole, to treat Chagas disease, which has now become commercially available in the United States.

Two antiparasitic medications, benznidazole and nifurtimox, are used for the treatment of acute, congenital, and chronic Chagas disease infections; however, until recently, they were exclusively available in this country only through the CDC’s Investigational New Drug (IND) program. New information published in the CDC’s Morbidity and Mortality Weekly Report detailed the characteristics of patients included in the IND program from 2011 to 2018.

Most patients [361 of 369] who received benznidazole through the IND program were adults who had become chronically infected with Chagas disease. A total of 319 (87.4%) patients were born in 1 of 12 Latin American countries, primarily El Salvador, Mexico, Bolivia, Guatemala, and Honduras. Of the 43 patients in the program born in the United States, at least 50% likely contracted Chagas disease from autochthonous, presumptive vector-borne transmission, the authors said in the report noted. The median age of patients in the program was 42.9 years; 34 patients were under age 19 years, including one 9-year-old patient, one 5-year-old-patient, and one newborn with congenital infection.

“The FDA’s approval of benznidazole and the commercial availability of the approved product in the United States likely will increase awareness of Chagas disease and make it easier for patients with the disease to get this therapy, regardless of where they acquired the infection,” explained lead author Barbara Herwaldt, MD, medical officer of the CDC’s parasitic diseases branch. In an interview with Contagion®, Dr. Herwaldt noted that the approval will increase access to treatment for Chagas disease patients in the United States.

The death prompted an investigation led by Ruchika Goel, MD, MPH, an assistant professor of pathology, laboratory medicine, and pediatrics at New York-Presbyterian Hospital, Weill Cornell Medicine.

In April 2017, the man, who had a history of health issues including homozygous factor XI deficiency, coronary artery disease, congestive heart failure, diabetes, anemia, and chronic kidney disease, was admitted to the hospital for transurethral resection of the bladder due to a urologic malignancy.

While hospitalized, he was diagnosed with iron deficiency, and his recovery was complicated by recurrent hematuria and symptomatic anemia. He was given 12 units of leukoreduced, irradiated erythrocytes, as well as 14 plasma transfusions to keep his factor XI levels above the hemostatic threshold, the authors noted in the case report.

Twenty days into his hospital stay, something changed. The man started running a fever and developed tachycardia and hypotension. He was given broad-spectrum antibiotics, but his condition worsened, even as his blood, urine, and throat cultures remained negative. After 4 days of fever, clusters of bacteria within neutrophils were seen on peripheral smears, a sign of A. phagocytophilum. He was started on doxycycline immediately, but soon went into refractory shock and suffered multiple organ failure. The patient died within 24 hours of the start of doxycycline treatment. An autopsy and blood samples later confirmed the infection and the diagnosis of human granulocytic anaplasmosis (HGA).

Because anaplasmosis is a tick-borne illness, investigators considered whether the patient may have contracted HGA from a tick bite, but this was quickly ruled out.

“Although the season was early spring, the likelihood of tick-bite transmission was extremely low, as the patient had been homebound for weeks before admission and had no pets (thus eliminating tick exposure via household pets),” Dr. Goel and colleagues wrote. “We pursued an investigation for transfusion-transmitted infection.”

Upon analysis, 1 of the 12 donor units tested positive for A phagocytophilum DNA.

The donated erythrocyte unit had been in storage for 22 days at the time of the transfusion, but it had cleared pretransfusion screenings. The donor later stated he experienced a rash and headaches around the time of donation, but no fever. The donor also did not report any illnesses in the days following the donation. The donor had been treated for Lyme disease, another tick-borne illness, although the exact details of that treatment were unavailable to investigators.

Most patients with HGA do not die from the infection: 31% are hospitalized, 7% end up in the intensive care unit, and 0.6% die. However, rates of death are 16 times higher in patients with immunosuppressive conditions.

According to the investigators, there is little to be done to prevent such cases. No US Food and Drug Administration–approved test exists to screen donated blood for A phagocytophilum, and donors generally are not asked whether they have ever been bitten by a tick.

No method of pathogen reduction is available for erythrocytes, either, although the investigators noted that such a process would likely have prevented the HGA transmission in this case.

The best way to minimize risk is for physicians to be cautious about their use of transfusions, according to the investigators.

“The most prudent approach to reduce the risk of transfusion-transmitted anaplasmosis is by the judicious use of blood components and the strict avoidance of unnecessary transfusions in adherence with published guidelines,” Dr. Goel and colleagues concluded. “This fatality from transfusion-transmitted anaplasmosis is a reminder of the serious residual risks from transfusions, as well as the increasing prevalence of A phagocytophilum.”

Posttransfusion Anaplasmosis Case Highlights Need for Vigilance in Transfusions
By Jared Kaltwasser

A new report on the case of a 78-year-old man who died of anaplasmosis following a blood transfusion highlights the risks of these procedures and the need for judiciousness when ordering them, according to a new report.

The death prompted an investigation led by Dr. Goel and colleagues, published in the August issue of Clinical Infectious Diseases. The best way to minimize risk is for physicians to be cautious about their use of transfusions, according to the investigators.

“The most prudent approach to reduce the risk of transfusion-transmitted anaplasmosis is by the judicious use of blood components and the strict avoidance of unnecessary transfusions in adherence with published guidelines,” Dr. Goel and colleagues concluded. “This fatality from transfusion-transmitted anaplasmosis is a reminder of the serious residual risks from transfusions, as well as the increasing prevalence of A phagocytophilum.”
New Aggressive Tick Species Is Spreading Through the United States

By Kristi Rosa

A tick species native to Australia, New Zealand, and eastern Asia newly emerged in several US states this summer, prompting health officials to warn the public to take protective measures against potential bites.

The tick (*Haemaphysalis longicornis*), referred to as the “long-horned tick” or “bush tick,” was first identified in New Jersey in November 2017 on a sheep in Hunterdon County. Since then, the tick has been detected in New Jersey’s Union and Middlesex counties as well, according to the New Jersey Department of Agriculture.

The tick has also been reported in 8 other US states. Virginia was the second to detect its presence, on an orphaned calf on a beef farm in Albemarle County. The National Veterinary Services Laboratory (NVSL) in Ames, Iowa, confirmed its presence on May 14, 2018. Soon after, on May 21, 2018, NVSL confirmed the tick’s presence in West Virginia, after 2 samples were collected from cattle on 2 different premises in Hardy County. The farms from which the samples were collected are located near the border of Virginia, about 100 miles from Albemarle County.

“This tick has been associated with bacterial and viral tick-borne disease in other parts of the world,” Miguela Mark-Carew, PhD, director of epidemiology and prevention services for the West Virginia Department of Health and Human Resources, Bureau for Public Health, stressed in a statement. “Like deer ticks that transmit Lyme disease, long-horned ticks are very small and can be difficult to find on people and animals. It is important to conduct full-body tick checks when returning from time outdoors in wooded areas.”

The US Department of Agriculture (USDA) confirmed the presence of the exotic tick in Arkansas on June 5, 2018, where it was found on a dog in Benton County. The tick was collected and submitted through a research project at Oklahoma State University, then confirmed by the NVSL via photograph and molecular typing. Then, on June 25, the tick was discovered in North Carolina on an opossum in Polk County and confirmed by NVSL.

New York was the next state to report the tick species in several locations throughout Westchester County. In collaboration with investigators from Fordham University and the Lyme Disease Diagnostic Center of New York Medical College, the New York State Department of Health identified the ticks, and the Rutgers University Center for Vector Biology and the USDA confirmed them.

Pennsylvania reported the tick in Centre County’s Potter Township on an adult male wild white-tailed deer that had been euthanized on July 10 by the Game Commission because it was exhibiting signs consistent with chronic wasting disease. The Southeastern Cooperative Wildlife Disease Study in Athens, Georgia, collected the deer’s ticks; NVSL confirmed that they were long-horned ones.

The Maryland Department of Natural Resources reported the state’s first sighting of this tick species on a white-tailed deer in Washington County; the tick’s presence was confirmed on July 27.

To date, no direct links among the 8 states’ cases are known.

The USDA warns that the tick poses a serious threat to livestock because heavy infestations can result in stunted growth, decreased production, and animal deaths. The current host list for this tick includes dogs, cows, goats, sheep, white-tailed deer, opossums, raccoons, and horses. The adult long-horned tick is described as dark brown in color and very difficult to see with the naked eye; however, when fully engorged, it is known to grow to the size of a pea.

“It is an aggressive biter and frequently produces significant infestations on domestic hosts, causing great stress, reduced growth and production, and exsanguination,” North Carolina Cooperative Extension officials warned in a statement. “As the tick can reproduce parthenogenetically (without a male), a single fed female tick can create a local population quickly.”

The tick is susceptible to common acaricides used to control other tick species in the United States; however, because it may infect any of several hosts, managing the species and eliminating it from an environment will be challenging.

Physicians should urge patients to use standard tick avoidance strategies and farmers should work with their veterinarians to check their livestock for ticks and ensure that parasite control plans are in place. If a long-horned tick is suspected, collect the tick for animal health officials to identify.

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**2018-2019 Flu Vaccine Recommendations From ACIP**

By Danielle Mroz, MA

Among new recommendations from the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) is that health care providers have the intramuscularly administered live attenuated influenza vaccine (LAIV) among their arsenal of available vaccines for the 2018-2019 flu season.

Although previous LAIV vaccines were found to have poor effectiveness against influenza A (H1N1) pdm09-like viruses, they proved effective against influenza B viruses, and manufacturer data suggest that the new H1N1 pdm09-like virus included in the 2018-2019 vaccine “has improved replicative fitness over previous H1N1 pdm09-like viruses included in LAIV,” according to CDC’s Morbidity and Mortality Weekly Report.

The types of available vaccines for the 2018-2019 flu season include the LAIV and recombinant influenza vaccine (RIV) as quadrivalent vaccines, and inactivated influenza vaccines (IIVs) as both a high-dose IIV trivalent and adjuvanted IIV trivalent.

The influenza strains to be included in the trivalent vaccines include the following:

- **Influenza A/Michigan/45/2015 (H1N1) pdm09-like virus**
- **Influenza A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus**
  - Replaces A/Hong Kong/4801/2014 (H3N2)-like virus from the 2017-2018 Northern Hemisphere influenza vaccine
- **Influenza B/Colorado/06/2017-like virus**
  - Replaces B/Victoria/2/87 lineage
- **Influenza B/Brussels/60/2008-like virus**
  - Replaces B/CG/30/04 lineage

Influenza strains to be included in the quadrivalent vaccines are similar to the trivalent, plus:

- **Influenza B/Phuket/3073/2013-like virus**
  - B/Yamagata/16/2088 lineage

For patients who receive the LAIV, the effectiveness of the vaccine may be reduced if influenza antiviral medications are taken 48 hours prior, or up to 14 days after, vaccination. Patients vaccinated with the LAIV who take antivirals during those time periods may be revaccinated with another appropriate vaccine.

Individuals with a history of egg allergy, regardless of severity, can receive “any licensed, recommended, and age-appropriate influenza vaccine (IIV, RIV, or LAIV),” according to the updated recommendations.
minoglycosides date back to the 1940s, with the introduction of streptomycin. Streptomycin was the first antibiotic available for the effective treatment of tuberculosis, netting its discoverer, Selman Waksman, a Nobel Prize. During the golden age of antibiotic development in the 1940s through 1960s, minoglycosides continued to advance, along with many novel classes of antibiotics. Because of their potent activity against gram-negative organisms, minoglycosides became mainstays of infectious diseases pharmacotherapy, before eventually being displaced by broad-spectrum β-lactams, which became widely available in the 1980s and 1990s.

Inevitably, organisms developed resistance mechanisms to minoglycosides. In Enterobacteriaceae, resistance is commonly due to plasmid-encoded minoglycoside-modifying enzymes (AMEs). These enzymes cause a change in the chemical structure of the minoglycoside compound, resulting in lower binding affinity for the bacterial ribosome and high-level resistance to the class. Plazomicin, which was approved by the US Food and Drug Administration (FDA) on June 25, 2018, for the treatment of complicated urinary tract infections (cUTIs), was developed with structural modifications to protect it from AMEs. On August 3, 2018, the Centers for Medicare & Medicaid Services granted plazomicin a new technology add-on payment for inpatient use.

Plazomicin is active against all minoglycoside-modifying enzymes that confer resistance to older minoglycosides, except N-acetyltransferase exhibited in Providencia species. Compared with older minoglycosides, it has more potent activity against extended-spectrum β-lactamase–producing and carbapenem-resistant Enterobacteriaceae (CRE). In an in-vitro comparison with CRE, plazomicin had a minimum inhibitory concentration for 90% of the isolates (MIC90) of 2 mg/mL compared with gentamicin (MIC90 64 mg/mL), tobramycin (MIC90 32 mg/mL), and amikacin (MIC90 32 mg/mL). The approved breakpoint for plazomicin is 2 mg/mL.

To date, plazomicin has been studied in 2 significant phase 3 clinical trials. The EPIC trial compared plazomicin with meropenem for the treatment of cUTIs, including acute pyelonephritis (AP), in 388 adults. Plazomicin demonstrated noninferiority in composite cure, defined as achieving microbiologic eradication and clinical cure, at the test-of-cure visit with a success rate of 81.7% compared with 70.1% with

Plazomicin: A Novel Aminoglycoside

The drug presents a new option for patients at high risk of infections caused by organisms, such as carbapenem-resistant Enterobacteriaceae.

BY MARIA HEANEY, PHARMD, and JASON C. GALLAGHER, PHARMD, FCCP, FIDSA, BCPS

Plazomicin has shown potent activity against extended-spectrum β-lactamase-producing Enterobacteriaceae.

Aminoglycosides: A Novel Aminoglycoside
meropenem, a difference of 11.6% (95% CI, 2.7 to 20.3). Interestingly, patients in the plazomicin arm also experienced a significantly lower rate of clinical relapse at late follow-up compared with those in the meropenem arm (1.8% vs 7.9%). The FDA granted plazomicin approval for the treatment of cUTI including AP in adults 18 years and older with limited or no available treatment options. The indicated dose is 15 mg/kg intravenously every 24 hours.

Plazomicin was also studied in the CARE trial, a prospective, randomized study of patients with CRE infections. Investigators compared plazomicin with colistin in 37 adult patients with bloodstream infections (BSIs), hospital-acquired pneumonia, and ventilator-associated pneumonia caused by CRE. Patients in the plazomicin arm had a 26.5% lower all-cause mortality or disease-related complication rate compared with those in the colistin arm (23.5% vs 50.0%; 95% CI, −0.7 to 51.2). Patients treated with plazomicin for a BSI demonstrated a survival benefit with a hazard ratio for death of 0.37 (90% CI, 0.15 to 0.91). In addition, patients with a BSI had a microbiologic response rate of 92.9% when treated with plazomicin compared with 53.3% for those treated with colistin.

Following a single 15-mg/kg intravenous (IV) dose, plazomicin achieved a maximum concentration of 73.7 mg/mL, a minimum concentration of 0.3 mg/mL, and an area under the curve of 257 mg/mL. The mean volume of distribution is 17.9 L, and protein binding is estimated to be 20%. Plazomicin has a half-life of 3.5 hours in patients with normal renal function and is primarily excreted renally unchanged. Therapeutic drug monitoring can be performed, with a goal trough level of less than 3 mg/mL prior to the second dose to minimize toxicity. Plazomicin lung penetration was measured at 13% after a single dose in healthy volunteers.

Warnings and precautions associated with plazomicin use are consistent with those reported for older aminoglycosides. Black box warnings include nephrotoxicity, ototoxicity, neuro-muscular blockade, and teratogenicity. Adverse events most commonly observed in clinical studies include acute kidney injury, diarrhea, headache, nausea, vomiting, and hypertension or hypotension. In the EPIC trial, 3.7% of patients treated with plazomicin had a serum creatinine level increase of ≥0.5 mg/dL while on IV therapy compared with 3.0% of patients treated with meropenem. In the CARE trial, 11.1% of patients who received plazomicin had serum creatinine level increases compared with 38.1% of those who received colistin.

With its activity against multidrug-resistant Enterobacteriaceae, plazomicin offers an alternative for patients at high risk for, or with a history of, infection caused by organisms such as CRE. Although plazomicin is indicated by the FDA to treat cUTI, there are limited prospective data supporting its use as a treatment for other infections caused by CRE, particularly BSIs. As such, plazomicin may be particularly useful in urosepsis, though its use should be reserved for instances including carbapenem resistance or elevated MICs to older aminoglycosides. References available at ContagionLive.com.

*Active members of the Society of Infectious Diseases Pharmacists (SIDP)
Enhanced transmission electron micrograph of the Zika virus.by James Cavallini/ Science Source

(continued from cover)

especially those with a tropical climate.

First some numbers: As of September 5, 2018, just 41 cases of Zika had been confirmed in US states, all in individuals who were returning from travel to affected areas. In all US territories, which include Puerto Rico and the US Virgin Islands, there were 82 cases as of September 5.¹

Last year, there were 452 confirmed cases in US states, with 666 in all US territories.² Given that 5168 cases were reported in the states and 36,512 in the US territories in 2016, it’s clear that the impact of the virus is much lower now.³ Still, virus activity continues in the Caribbean, most of Latin America, Central Africa, India, Indonesia, Malaysia, Cambodia, and Papua New Guinea, among other places.⁴

Although Zika cases continue to be reported, the epidemic has been declared over in Puerto Rico, according to Contagion® Editorial Advisory Board member Carmen Zorrilla, MD, professor of obstetrics and gynecology at the University of Puerto Rico School of Medicine in San Juan. “We knew there was an epidemic when people presented with rash and symptoms, even nonpregnant ones,” Dr. Zorrilla told Contagion®. “We’re not seeing that [now].”

Other experts agree. “Because we have fewer cases now, our attention span is a little limited,” said Thais dos Santos, MS, advisor on surveillance and control of arboviral diseases in the Neglected, Tropical and Vector-Borne Diseases Unit of the Communicable Diseases and Environmental Determinants of Health Department, a division of the Pan American Health Organization, in an interview with Contagion®. “It’s kind of fallen off a lot of people’s radar. But the virus itself isn’t any less dangerous. The virus hasn’t become less aggressive.”

According to Ms. dos Santos, in the Caribbean and Latin America (Brazil was at the epicenter of the crisis), many individuals may have become naturally immunized against the Zika virus as it swept through these regions, contracting it without necessarily even knowing it. Because only 20% to 40% of infected people ever show symptoms,⁵ she said, Zika often escapes notice.

Kate Fowlie, a spokeswoman for the US Centers for Disease Control and Prevention (CDC), agrees that natural immunity is the reason for the disease’s current low numbers.
“We expect fewer Zika cases in 2018 because a proportion of the population was infected in 2016 and is no longer susceptible to infection,” she said. “However, mosquito-borne disease outbreaks are difficult to predict. There will be future outbreaks, including large ones, as well as years with reduced transmission, but it is impossible to know when or where these transmission patterns will occur.”

Dr. Zorrilla, however, is not sure widespread immunity is the reason for Zika’s quieting in Puerto Rico. “I calculated that about 10.5% of the pregnant women in Puerto Rico had a positive test for Zika,” she said. “That is not enough to cause herd immunity.” Her theory is that, much like dengue and other tropical diseases, Zika is following a natural cycle that ebbs and flows. “It seems that these vector disease epidemics...come in waves for periods of 3 to 5 years. The vector [the mosquito] is there. It’s a matter of time. We need to watch for the emergence of a new epidemic.”

But predicting when and if a Zika epidemic will hit is not simple. “This is a really difficult disease to do surveillance for,” Ms. dos Santos pointed out. According to her, of those who do experience the typical complaints of rash, fever, muscle weakness, and inflamed eyes (conjunctivitis), only up to half—and possibly significantly fewer—bother to seek treatment. “The signs and symptoms of people who have Zika are very nonspecific,” she said. In other words, the disease can easily be confused with something else, such as a cold or a mild case of influenza.

DEVASTATING CONSEQUENCES
As we now know, Zika’s all-too-easily missed symptoms may give no indication of its potentially serious complications. Currently, there is no treatment for Zika. Women who contract the virus are, if they are of childbearing age, at risk of giving birth to children with severe health problems including microcephaly, eye problems (including vision loss), epilepsy, nervous system defects, and hearing defects. An August 2018 Morbidity & Mortality Weekly Report from the CDC revealed that of 1450 children born to mothers known to have the Zika virus during pregnancy, 1 in 7 had a birth defect associated with the virus or a neurological abnormality possibly linked to the virus (or both). Experts fear the true toll of the disease could be even higher as children age. “We’re only beginning to scratch at the surface of the impact of this,” Ms. dos Santos explained.

Although rare, Guillain-Barré syndrome (GBS) is also a known risk of Zika. This nervous system malady can strike anyone and causes muscle weakness or, in its most extreme form, complete paralysis that can last up to several months. According to Dr. Zorrilla, GBS can result from a number of diseases, including dengue and influenza, but when it results from the Zika virus, it appears to manifest in a more severe form.

Whether of childbearing age or not, individuals traveling to or residing in places that saw a lot of Zika activity in the past couple of years should not be lulled into complacency by the drop-off in the number of cases, say many experts. Although another large epidemic is unlikely in the short term, infections are still taking place. “The continental United States and Hawaii will continue to see some travel-related cases, and local transmission is possible because the types of mosquitoes that carry Zika virus are present across a large portion of the United States,” said the CDC’s Ms. Fowlie. “As travelers visit countries with risk of Zika, they can be infected and bring the virus back to the United States, where it could be spread to local mosquitoes or to others through sex.”

The possibility of sexual transmission means that individuals must be very careful in their intimate relationships. The CDC has issued updated guidelines, including the recommendation that any man who might have been exposed to Zika avoid conceiving for at least 3 months after his symptoms start. (Initially, men were told to wait 6 months before trying to conceive with a partner.) This is because women are at risk of getting the virus from their partner’s semen, which can harbor it for several months. Women who are already pregnant are also at risk if they engage in unprotected sex with a potentially infected partner, so use of a condom or abstinence is encouraged until the birth. The exact amount of time someone remains infectious after acquiring the virus is unknown.

According to Ms. Fowlie, the CDC received $350 million from the 2016 federal budget and used it to “prevent, detect, and respond to Zika,” she said. “CDC’s funding was used to increase mosquito control and surveillance, laboratory capacity, public health studies, technical assistance to state and local governments, and diagnostic development.” Some of the money went toward preventive measures, such as the spraying of insecticides to reduce the insect population in locales that have had disease activity. In some tropical locations without air-conditioning, places where people rely on open or poorly screened windows for ventilation, officials distributed Zika prevention kits that contained bed netting to help keep mosquitoes away during sleep. The kits also included condoms, mosquito repellent, and standing-water treatment tablets that kill mosquito larvae in puddles.

But the one thing that might make a real impact on Zika transmission rates, a vaccine, has yet to be approved by the US Food and Drug Administration. The National Institute of Allergy and Infectious Diseases reports that several types of vaccines are in development and will potentially be used to prevent Zika infection. They include vaccines based on DNA, inactivated Zika, and live Zika. Also in development is a vaccine that should offer protection against a variety of mosquito-borne diseases, including Zika. Most are in the clinical testing phase right now, and the medical community hopes they will be available sooner than later.

References are available at ContagionLive.com.
Managing lower respiratory tract infections is a key focus of antimicrobial stewardship efforts to curb the spread of drug-resistant pathogens.

Antimicrobial resistance is a growing threat to public health. According to the US Centers for Disease Control and Prevention, at least 2 million Americans contract an antibiotic-resistant bacterial infection each year, and about 23,000 of these patients die.1

The antibiotic resistance crisis has arisen because of antibiotic overuse and misuse,2 and antimicrobial stewardship (AMS) represents a vital initiative to help combat it. AMS is composed of coordinated strategies designed to improve the appropriateness of antimicrobial use, aiming not only to reduce resistance to antimicrobial agents but also to enhance patient care.2

Interventions are especially needed to improve antibiotic use for common indications such as lower respiratory tract infections (LRTIs). These infections are a major public health problem in many countries, causing significant morbidity and mortality.3 And, according to Mary A. Musgrove, PharmD, of Henry Ford Hospital, Detroit, Michigan, and colleagues, about one-third of antibiotics administered in US hospitals are used to treat LRTIs.4

In an interview with Contagion®, Susan L. Davis, PharmD, also of Henry Ford Hospital, said that antimicrobial therapy in pneumonia is largely empiric. “Decisions about de-escalation can be difficult when the pathogen isn’t clear,” she said, “which creates some challenges for antimicrobial stewardship programs.”

Treatment decisions should be data driven
Antibiotic prophylaxis is an important component of antibiotic use in LRTIs that deserves evaluation in the ongoing effort to curb antibiotic resistance. In particular, clinicians’ decisions to administer prophylactic antibiotics to patients with LRTIs should be evidence based, to avoid exposing patients to potentially unnecessary antibiotics. Although often used in patients with aspiration pneumonitis, antibiotic prophylaxis has not been shown to prevent development of aspiration pneumonia or reduce mortality.5 However, data show that more than three-fourths of critical care physicians continue to routinely prescribe antibiotics for patients who have experienced an aspiration event but who do not have an associated infection.6

Improving Antimicrobial Stewardship in the Management of Respiratory Infections
As knowledge and awareness of rising antimicrobial resistance increase, clinicians must continue to adopt strategies for improving antibiotic use.

By Nicola M. Parry, BVSc, MRCVS, MSc, DACVP, ELS

Dr. Parry, a board-certified veterinary pathologist, graduated from the University of Liverpool in 1997. After 13 years in academia, she founded Midwest Veterinary Pathology, LLC, where she now works as a private consultant. Dr. Parry writes regularly for veterinary organizations and publications.
Although pneumonitis and pneumonia are both potential sequelae of aspiration, they are different clinical syndromes. Aspiration pneumonitis represents an acute chemical-induced injury that results when reflux and inhalation of harmful fluids—most typically, sterile acidic stomach contents—cause acute inflammation in the lung. In contrast, aspiration pneumonia represents an acute lung infection that results from aspiration of a large volume of colonized oropharyngeal material.

In a recent study in patients with acute aspiration pneumonitis, Jerome A. Leis, MD, MSc, of the University of Toronto, Ontario, Canada, and colleagues showed that giving prophylactic antibiotics within 48 hours of an aspiration event does not provide mortality benefit. Instead, this practice leads to more frequent antibiotic escalation and fewer antibiotic-free days among those patients who do go on to develop aspiration pneumonia.

Dr. Leis and colleagues performed a retrospective cohort study of 200 patients with acute aspiration pneumonitis to investigate the harms and benefits of prescribing antibiotics in these cases. They examined the patients’ clinical outcomes, comparing the findings among those who received prophylactic antibiotics during the first 2 days after an acute macroaspiration event, with those among patients who received standard supportive care.

Of the 200 patients, 76 (38%) received prophylactic antibiotics and 124 (62%) received only supportive care. The investigators found that unadjusted in-hospital mortality was similar in both groups of patients (25% vs 25%). However, although patients receiving prophylactic antibiotics were not less likely than those receiving standard care to be transferred to critical care (5% vs 6%; P = .7), they had fewer antibiotic-free days (7.5 vs 10.9; P < .0001) and more frequently required their antimicrobial agent to be switched to a new one with a higher spectrum level (8% vs 1%; P = .002) up to 2 weeks after the aspiration event.

Even when the investigators adjusted their analysis for patient characteristics that predicted 30-day mortality (eg, age, being admitted to the medicine service rather than to surgery), antibiotic prophylaxis still did not provide mortality benefit (odds ratio, 0.9; 95% CI, 0.4-1.7; P = .7).

Overall, this study highlighted the lack of clinical benefit provided by antibiotic prophylaxis in patients with acute aspiration pneumonitis. It also showed that this practice may even create selective pressures that result in the later need to give more antibiotics—often agents with a broader spectrum of activity—to those patients who go on to develop aspiration pneumonia.

Therefore, standard supportive care should “remain the mainstay of management of patients with acute aspiration pneumonitis following a macroaspiration event,” Dr. Leis and colleagues said.

**THE ROLE OF THE CLINICAL MICROBIOLOGY LABORATORY IN AMS**

In another recent study, Dr. Musgrove and colleagues explained that the challenge of antibiotic prescribing for LRTI has been compounded by health care–associated pneumonia (HCAP) criteria defined in the 2005 Infectious Diseases Society of America and American Thoracic Society pneumonia guidelines. “These HCAP criteria had an unintended consequence of excessive use and continuation of empiric antibiotics targeting methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*,” the authors wrote.

Because microbiology results play a critical role in guiding clinicians’ antimicrobial prescribing practices, the authors stressed that clinical microbiology laboratories can thus also contribute to AMS efforts.

“The language of microbiology results has previously been demonstrated to influence prescriber behavior,” Dr. Musgrove and colleagues said. “Some of these changes can be implemented with few additional resources.” Such simple interventions that change clinicians’ prescribing behavior in a way that guides them to select more appropriate antimicrobial therapy are often described as nudges.

With this in mind, Dr. Musgrove and colleagues performed a quasi-experimental study to investigate the effect of introducing a change in microbiology reporting on respiratory cultures growing commensal flora. They implemented this reporting change in May 2016, after which time reports for these respiratory cultures specified “commensal respiratory flora only: No *S. aureus*/*MRSA or *P. aeruginosa*.”

The investigators evaluated data from 105 patients during a 6-month period before the intervention was introduced (preintervention group) and from an additional 105 patients during a corresponding 6-month period after it was introduced (intervention group).

They found that including this simple comment to more clearly communicate respiratory culture results for normal flora positively affected clinicians’ prescribing practices. Clinicians more commonly de-escalated/discontinued use of unnecessary broad-spectrum antibiotics for patients in the intervention group than for those in the preintervention group (73% vs 39%; P < .001). “[T]he intervention comment was associated with a 5.5-fold increased odds of deescalation,” the authors wrote. Post intervention, clinicians also reduced their prescribing of anti-MRSA and antipseudomonal therapy from a median of 7 days to 5 days (P < .001).

Also, fewer patients in the intervention group experienced acute kidney injury (31% vs 14%, P = .003). However, introducing the intervention did not result in any significant difference in all-cause mortality (30% vs 18%, P = .052).

“Stewardship interventions don’t have to be complicated to change behavior,” said Dr. Davis. “This was a simple change to highlight the meaning of the phrase **commensal flora**, which not everyone understood previously.”

“This intervention helps demonstrate the profound importance of clinical microbiologists in antimicrobial stewardship. Working with them to clearly communicate test results and interpretation can make a big impact on patient care and antibiotic prescribing,” she said.

Because improper antibiotic use can have unintended consequences, the results of these 2 studies in patients with LRTIs highlight the importance of appropriate AMS, including a collaborative approach at all levels of patient care, in tackling this major public health issue.
Guideline Updates for the Treatment of Adolescents and Adults With HIV
Revised DHHS and IAS–USA guidelines provide new insight for physicians managing patients with HIV.

BY AMY C. MIN, PHARMD, BCACP, AAHIVP*

The availability of more treatment options for HIV has made management of infections easier than ever before. With over 45 individual and fixed-dose combination antiretroviral (ARV) agents approved by the US Food and Drug Administration, providers are able to select the ARV regimens best suited for the patient, and selection of antiretroviral therapy (ART) should be based on updated guideline recommendations. Several guidelines on the treatment and management of HIV infection are available, including but not limited to those by the US Department of Health and Human Services (DHHS), the International Antiviral Society–USA Panel (IAS–USA), the European AIDS Clinical Society (EACS), the British HIV Association (BHIVA), and the World Health Organization.1-6 These guidelines are routinely updated to reflect the current literature available.

Recent updates to the DHHS and IAS–USA guidelines, as well as similarities and differences between the 2 sets, will be discussed in this article.

HIGHLIGHTS OF THE DHHS GUIDELINES
The DHHS guidelines for the use of ARV agents in adults and adolescents living with HIV were updated in May 2018. Many providers refer to these guidelines because of the extensiveness of their coverage of both treatment and management recommendations for people living with HIV. The update included new data on dolutegravir and added bictegravir to the list of recommended initial regimens for HIV. Additional recent updates to HIV treatment can be reviewed in the guidelines in the section, “what to start.”7

Recent preliminary study results from a National Institutes of Health (NIH)–funded observational surveillance study in Botswana revealed possible risks associated with taking dolutegravir prior to pregnancy and through conception.7 The study identified 4 infants with neural tube defects out of 426 infants born to women living with HIV who had initiated dolutegravir prior to pregnancy and continued it through time of conception. The rate of neural tube defects in infants born to mothers living with HIV taking dolutegravir from the time of conception was 0.94% (95% CI, 0.37 to 2.4) which was higher than the rates in those who started dolutegravir during pregnancy, 0.0% (95% CI, 0.0 to 0.13), and those who were on non-dolutegravir based ART, 0.12% (95% CI, 0.07 to 2.1).7 Based on this potential safety signal, the DHHS issued a statement regarding dolutegravir use in women of childbearing potential. A documented negative pregnancy test is recommended before providers initiate dolutegravir. If patients are pregnant and within 8 weeks from their last menstrual period, the risks and benefits of staying on a dolutegravir-based ART regimen versus switching to a non–dolutegravir-based ART regimen should be discussed. The risk of an embryo developing neural tube defects is highest while patients are on dolutegravir during the first 28 days after conception, prior to the time the neural tube closes in the embryo.8 Based on these new preliminary data, the DHHS recommend dolutegravir-based regimens be initiated only in patients who do not desire pregnancy and are on effective contraception.9 Additional specific recommendations can be found in the DHHS HIV treatment and perinatal guidelines.1,10 Final

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In its 2018 guidelines, the IAS–USA updated recommendations on CD4 cell count monitoring. CD4 cell count monitoring is recommended every 6 months until the patient reaches over 250 cells/μL maintained for at least a year; monitoring can then be discontinued as long as the patient is able to maintain viral suppression. This recommendation is based on studies whose results showed little added value of CD4 cell count monitoring when the viral load is suppressed. The DHHS HIV guidelines differ, as they recommend CD4 count monitoring every 3 to 6 months for the first 2 years of ART if patients are viremic or their CD4 count is less than 300 cells/μL. The DHHS guidelines recommend that after 2 years on effective ART with continued viral suppression, patients decrease CD4 monitoring to every 12 months if their CD4 count is between 300 and 500 cells/μL; optional CD4 count monitoring is recommended only if counts are above 500 cells/μL.

Another difference between the updated DHHS and IAS–USA guidelines is that the IAS–USA guidelines continue to recommend against MAC prophylaxis in patients with viral suppression on ART because of the low incidence and burden of disease in the United States. Patients living with HIV are at an increased susceptibility to MAC disease if their CD4 cell count falls below 50 cells/μL, if they have a high HIV viral load, or if they have had previous opportunistic infections. The DHHS guidelines recommend that once active disease is ruled out, a patient whose CD4 count falls below 50 cells/μL receive azithromycin 1200 mg weekly or clarithromycin 500 mg twice daily for MAC prophylaxis.

Both the DHHS and IAS–USA HIV guidelines recommend initiating ART as soon as possible after diagnosis. The IAS–USA guidelines more strongly recommend rapid initiation to include same-day starts in patients who are committed to starting ART. HIV PrEP recommendations differ between the guidelines, as well, with the IAS–USA guidelines incorporating newer data and recommending on-demand or event-driven PrEP (“2-1-1”) in men who have sex with men with infrequent sexual encounters as an alternative to daily PrEP for men who have sex with men (MSMs) with infrequent sexual exposures. The EACS and BHIVA guidelines also have similar recommendations for on-demand PrEP as an alternative to daily PrEP for MSMs. The PrEP guidelines which is a joint effort by the US Public Health Service with the Centers for Disease Control and Prevention, do not recommend on-demand PrEP due to lack of data of efficacy in heterosexual men and women and persons who inject drugs. Additionally, adherence outside of a trial setting has not been evaluated. Discussion of HIV PrEP is beyond the scope of this article, and the guidelines and literature should be consulted. These guidelines can also be found on the DHHS guideline website.

As the treatment and management of patients living with HIV continues to evolve and improve, the most updated versions of guidelines should be consulted. Both the DHHS and IAS–USA guidelines are commonly used in the United States and are updated on a regular basis. Although both guidelines provide similar recommendations, there are slight differences in each that provide different perspectives in the management and prevention of HIV.

References available at ContagionLive.com.
The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) updated the hospital-acquired and ventilator-associated pneumonia (HAP, VAP) guidelines in 2016. HAP is defined as pneumonia not associated with mechanical ventilation that develops 48 hours or more after admission to a hospital. VAP is defined as pneumonia that develops 48 to 72 hours after endotracheal intubation. HAP and VAP account for 22% of all hospital-acquired infections and lead to significant morbidity, mortality, and health care costs. Major differences between the 2005 and 2016 guidelines include removal of health care–associated pneumonia (HCAP), the addition of biomarker (eg, procalcitonin) usage recommendations for assisting with duration of therapy, and redefinition of duration for most patients from between 8 and 15 days to 7 days. In addition, Grading of Recommendations Assessment, Development and Evaluation methodology was instituted in the new guidelines. In terms of double coverage for \textit{Pseudomonas aeruginosa}, fewer risk factors to warrant combination were mentioned in the 2016 guidelines.\cite{1,2}

**REMOVAL OF HCAP FROM 2016 GUIDELINES**

The elimination of HCAP from inclusion in these guidelines was due to 2 main reasons: (1) Many patients presenting from nursing homes or other health care facilities still have community-acquired pneumonia (CAP) with nonresistant pathogens, and (2) these patients are from the community and present to emergency departments, and their management is thus better managed using the CAP guidelines, which we are still anxiously awaiting.

The 2005 guidelines suggested that patients who were exposed to any health care environment (eg, nursing homes, rehab centers) were at risk for multidrug-resistant organisms (MDROs). However, the supporting studies were poorly designed and highly biased (ATS/IDSA 2005).\cite{3} Since then, studies assessing true risk of acquiring MDROs have concluded that patient characteristics (eg, presence of indwelling urinary catheters, recent antibiotic usage in the prior 90 days, previously known \textit{Pseudomonas} colonization, or prolonged prior hospital admission) likely play a much larger role in predicting MDRO risk.\cite{4}
MULTIDRUG-RESISTANT INFECTIONS

MICROBIOLOGIC DIAGNOSIS OF PNEUMONIA
The 2016 IDSA HAP/VAP guidelines place an emphasis on noninvasive respiratory sampling, but it is important to consider these cultures in clinical context, given that the specificity of semiquantitative respiratory cultures is around 50%. This is obvious in the guideline setting but not always considered in real practice, where cultures may be obtained as part of a fever work-up but not out of clinical concern for HAP/VAP specifically. In clinical practice, we know that many of our critically ill and chronically ill patients may have abnormal chest imaging at baseline for reasons other than pneumonia, making the distinction of respiratory colonization versus true infection more difficult. However, the consideration of other clinical factors such as oxygen requirement changes, hemodynamic instability, and changes in secretions may help a discerning clinician.

USE OF BIOMARKERS
The 2016 guidelines suggest the benefit of using procalcitonin in addition to clinical criteria to guide duration of therapy (but not to aid in diagnosis of pneumonia). The major benefits in limiting duration of therapy, when appropriate, include reduced antibiotic-related adverse effects; sooner reconstitution of gut flora, thereby reducing risk of Clostridium difficile-associated diarrhea and other superinfections; and cost reduction.

DURATION OF THERAPY
The 2016 guidelines recommend 7 days for both HAP and VAP treatment unless there are complicating factors or slow clinical improvement. The evidence behind this new duration recommendation came primarily from 2 large systematic reviews assessing patients with HAP/VAP treated with short courses of antibiotics (7-8 days) versus long courses (10-15 days) and found no differences in mortality, recurrent pneumonias, length of stay, or duration of mechanical ventilation.

For VAP due to nonfermenting gram-negative rods, there was no difference in pneumonia recurrence or mortality. Thus, longer durations based solely on microbiologic species were not supported.

EMPIRIC COVERAGE
The 2016 guidelines highlighted the need to empirically treat all HAP/VAP patients with antibiotics that are active against both Staphylococcus aureus and P aeruginosa. If empiric methicillin-resistant S aureus (MRSA) coverage is necessary, vancomycin or linezolid should be used. Empiric MRSA treatment should be started if MRSA rates are more than 10% to 20% of all S aureus isolates in the specific unit or hospital at which the patient is being treated. For gram-negative coverage, β-lactams are preferred, although the specific agent of choice depends on local susceptibilities, ideally based on the unit antibiogram. Aminoglycosides should never be used as monotherapy for pneumonia because of increased mortality shown in prior studies.

DOUBLE COVERAGE AND MDRO RISK FACTORS
The 2016 guidelines recommend 2 antipseudomonal antibiotics from different classes if patients have MDRO risk factors or are in a unit where more than 10% of gram-negative isolates are resistant to the preferred agent (usually a β-lactam). MDRO risk factors are different for VAP and HAP; however, prior antibiotic use is significantly associated with acquisition of MDRO for both types of pneumonia. Additional factors specific to VAP may predispose patients to MDRO (see the 2016 guidelines for details).

Regardless, the double coverage suggestion is a weak recommendation, based on low-quality evidence. Therefore, in our opinion, it should be taken with a grain of salt. In fact, to our knowledge, there has never been a study whose results have shown a mortality benefit with addition of a second antipseudomonal agent. The second agent recommended is either a fluoroquinolone or an aminoglycoside because the two are the only non-β-lactam antibiotics currently available for the treatment of pneumonia. Aside from a low quality of evidence used to make this recommendation in the guidelines, many institutions face high rates of fluoroquinolone resistance, making the benefit of the addition of fluoroquinolones to β-lactam regimens for patients with HAP/VAP at hospitals with more than 30% to 40% gram-negative fluoroquinolone resistance essentially nil but with the higher risk of toxicity and C difficile infection. Combinatorial antibiograms are useful to identify whether fluoroquinolones or aminoglycosides remain active for β-lactam-resistant isolates. Although aminoglycosides, particularly amikacin, will likely target many β-lactam-resistant gram-negative strains, higher dosing is warranted for pneumonia. Even with higher dosing, aminoglycosides do not have optimal lung penetration and are not always feasible to initiate in older patients or those with renal dysfunction. However, in patients with concurrent gram-negative bacteremia or in septic shock, it may be prudent to add an aminoglycoside pending susceptibility results. The guidelines do not take into account the clinical stability of the patient.

VENTILATOR-ASSOCIATED TRACHEOBRONCHITIS
The guidelines also include discussion on the lack of high-quality evidence to support treating ventilator-associated tracheobronchitis (VAT) and, when weighing the risks associated with antibiotic usage (resistance, C difficile, etc), recommend against treating VAT. The only consistently significant benefit in the studies was a possible decrease in mechanical ventilation days, without benefits in mortality or length of stay.

In clinical practice, however, it is often difficult for clinicians to distinguish between pneumonia and VAT. This is particularly the case for patients with abnormal chest imaging at baseline because of chronic lung disease who may also have large oxygen requirements. These patients often get repeat courses of antimicrobials but likely do not experience much benefit.

CONCLUSIONS
The 2016 IDSA/ATS guidelines contain significant improvements compared with the 2005 guidelines, as more literature has been published regarding many important concepts. Although the new recommendations highlight the importance of antimicrobial stewardship by de-escalation when possible and shorter durations, diagnosis of pneumonia continues to be problematic, particularly in the hospital setting.

References are available at ContagionLive.com.
The globalization of antibiotic stewardship programs (ASPs) is necessary in the fight against antibiotic resistance. Individual countries must take meaningful actions to counter antimicrobial resistance (AMR), tailoring implementation according to their national circumstances. One of the key challenges is preventing the overprescription of antibiotics in hospitals. Every unnecessary dose of antibiotics contributes to the escalating rate of AMR. The unrestrained use of antibiotics is the main driver for the rise in drug-resistant infections, which now kill more than half a million people every year worldwide, including 50,000 in Europe and the United States combined. Despite efforts by the US Centers for Disease Control and Prevention, the World Health Organization, the United Nations (UN), and others to encourage more prudent use of antibiotics, an international team of investigators found a 65% rise in worldwide consumption of antibiotics from 2000 to 2015. The increase in 76 countries was driven almost entirely by rising use in low- to middle-income countries (LMICs). Of particular concern is the escalating global use of antibiotics of last resort, such as colistin. To address the overprescription of antibiotics in hospitals, we need a scalable and proven solution that can be implemented on a global basis.

GLOBAL CALL TO ACTION FOR ASP

The UN issued a call to action for countries to implement antibiotic stewardship to address AMR and overuse of antibiotics, although action to tackle AMR has not yet matched the scale of the threat. The problem is worse in LMICs. Building on current work supported by multiple organizations in the areas of surveillance and antibiotic resistance, implementation of ASPs to assure optimal use of antibiotics is equally important. Documenting antibiotic resistance rates from surveillance programs will not result in any meaningful change in antibiotic use if hospitals do not have trained health care providers who know how to apply surveillance data to make an antibiotic stewardship intervention at the point of care.

ASP IN LMICS

ASPs are desperately needed in hospitals; however, a shortage of adequately trained pharmacists and physicians in infectious diseases creates a challenge. Pharmacy practice models vary significantly in developing countries, with barriers to effective practice models including acute shortages of qualified pharmacists, no implementation of dispensing separation practices, and weak regulatory enforcement of drug sales. Pharmacists, while not always clinically empowered, are present in point-of-care moments and can help change physician behavior. Antibiotic stewards from resource-rich countries such as the United States must help LMICs implement ASPs. Elements of successful antibiotic stewardship in hospitals in LMICs have been developed by investigators working with 15 experts (including Dr. Goff) from 13 countries on 6 continents. Led by Céline Pulcini, a professor of infectious diseases in France and a member of DRIVE-AB (Driving Re-investment in R&D and Responsible Antibiotic Use), the consensus-based process produced 7 core elements (leadership commitment, accountability, drug expertise, action, tracking, reporting, and education) as well as 29 checklist items that are relevant in all settings, including those that are resource limited.

Globalization of Antibiotic Stewardship Programs: The World Is Waiting

Stewards from high-income countries must assist low- to middle-income countries in antibiotic stewardship.

BY DEBRA GOFF, PHARMD, FCCP*; ANGELIKI MESSINA, MSPHARM, BSPHARM*; AND EMILY HEIL, PHARMD, BCPS-AQ ID*
The slow implementation of antibiotic stewardship in LMICs means more patients die every day from untreatable infections. To guide the rational use of antibiotics in LMICs, standard treatment guidelines (STGs) have been developed by national thought leaders in several countries. These STGs, coupled with Essential Medicine Lists, are intended to promote equitable access to affordable medicines that are safe and effective and improve the quality of patient care and clinical decision making. Stricter oversight of antibiotics and compliance to STGs are warranted to reduce the amount of antibiotics consumed in LMICs. However, extensive data on the reporting of antibiotic use, consumption, and compliance with guidelines among hospitals and clinics are currently lacking. Pharmacists can play a key role in the implementation of surveillance systems for AMR and antibiotic use. As custodians of medicines, pharmacists are well placed to lead an antibiotic surveillance initiative, through not only audit and data collection but also relationship building and working in multidisciplinary teams. The Table provides 3 examples of US ASPs that are working with LMICs to implement or advance ASP, along with suggestions on how US stewards can affect global stewardship initiatives.

### ASPs in South Africa

The South African National Department of Health formalized and published a 10-year antimicrobial resistance national strategic framework (2014-2024) to align with international efforts aimed at curtailing the mounting rate of AMR. The strategy advocates for collaboration across multiple sectors and adopts a One Health approach in its methodology. Furthermore, it calls for strengthened global partnerships because the responsibility to cocreate solutions to this crisis is universally shared.

The Ohio State University antibiotic stewardship train-the-trainer program was initiated in South Africa in 2014. The program accelerated the uptake of antibiotic stewardship through exposure and mentorship of pharmacists and allowed for trained pharmacists to implement ASPs faster in their settings. Pharmacists (not formally trained in infectious diseases) decreased antibiotic use in 47 private hospitals across South Africa by 18% through implementation and monitoring of defined “low-hanging fruit” stewardship interventions including the prospective audit with intervention and feedback of antibiotic duration greater than 7 and/or 14 days, redundant duplicate antibiotic cover, cultures taken prior to antibiotic duration greater than 7 and/or 14 days, redundant duplicate antibiotic cover, cultures taken prior to antibiotic therapy, and the coadministration of 4 or more antibiotics. The train-the-trainer program shows potential to accelerate the global growth of antibiotic stewardship in every hospital.

In addition, the Wellcome Trust in London, England, produced a video (wellcome.ac.uk/news/three-pioneering-ways-stop-superbugs) in 2018 titled “South Africa: Empowering Hospital Pharmacists,” highlighting the work of South African pharmacists, some of whom completed the US train-the-trainer antibiotic stewardship mentoring program and are taking pioneering action to tackle AMR. By promoting pioneers in this way, national and global leaders in AMR now have the opportunity to identify how replicable, scalable best practices can form the foundations of a successful, coordinated global response.

### Zambia

Although formalized antimicrobial stewardship is in its infancy in Zambia, the country has taken major steps in response to the World Health Organization’s Global Action Plan for Antimicrobial Resistance, which calls on countries to develop their own action plans on antimicrobial resistance. In the fight against AMR, Zambia also adopted a One Health approach that includes the human, animal, agriculture, and environmental sectors with the release of its National Action Plan (NAP) in 2017. Afterward, a kick-off summit for antimicrobial stewardship was held and included leadership from the Ministry of Health along with physicians and pharmacists from local hospitals to begin implementation of the NAP. Speakers included representatives from South Africa and Uganda who shared their respective country’s experiences with stewardship implementation. The workshop was sponsored by the Zambia National Public Health Institute and ReAct Africa. ReAct is an independent global network for antimicrobial resistance led by pharmacist Mirfin Mpundu that provides support to national governments implementing antimicrobial resistance action plans.

University Teaching Hospital, the highest-level hospital in Zambia, has begun to gather baseline antibiotic usage and resistance data with physicians and pharmacists from the University of Maryland, Baltimore. The hospital will pilot stewardship interventions discussed at the summit, including some of the tools used in South Africa. Given the success and scalability demonstrated by the South African pharmacists, this initiative will likely serve as an important model for other countries in Africa.

### Conclusions

Aristotle said, “The whole is greater than the sum of its parts.” That is, when individual parts are connected to form 1 entity, they are worth more than if they had remained in silos. This quote reminds us that what 1 person can do, many can do better. There is something special that happens when ASPs from resource-rich countries work together with LMICs toward the common goal of decreasing antibiotic use and resistance. ▲

References are available at ContagionLive.com.

### Table. How US Stewards Can Support Global Stewardship Initiatives Without Travel

<table>
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<th>DOMAIN</th>
<th>EXAMPLES</th>
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| **Education**    | • Host Web-based teaching sessions via Skype or other free systems.  
|                  | • Join Twitter and participate in chats hosted by @ASP_CHAT, @SIDPharm, @accpinfdprn, and @CIDRAP_ASP.  
|                  | • Write educational blog articles on infectious diseases and stewardship topics (e.g. ID Stewardship; idstewardship.com).  
|                  | • Share new and applicable stewardship literature on social media platforms.  
|                  | • Share free online stewardship training and certification courses or platforms. |
| **Resources**    | • Publish stewardship research in open-access journals.  
|                  | • Provide open-access training materials:  
|                  | - US Centers for Disease Control and Prevention Training on Antibiotic Stewardship (train.org/cdctrain/training_plan/3697)  
|                  | • Provide open-access resources:  
|                  | - South African Antibiotic Stewardship Programme (fsdssa.co.za/SAASP)  
|                  | - University of Minnesota Center for Infectious Disease Research and Policy Antimicrobial Stewardship Project (cidrap.umn.edu/asp)  
|                  | - Nebraska Medicine Antimicrobial Stewardship Program (nebraskamed.com/for-providers/asp)  
|                  | - Johns Hopkins Medicine Antimicrobial Stewardship Program (hopkinsmedicine.org/amp/guidelines/)  
| **Mentorship**   | • Provide shadowing opportunities to stewards from other countries. |
Achieving antimicrobial stewardship programs’ primary goal of using antibiotics responsibly to optimize patient care and minimize development of resistant infections, requires education of and collaboration among multiple parties, including physicians, information technology (IT) specialists, hospital administrators, and patients, according to experts who participated in a Contagion Peer Exchange panel.

Jason Pogue, PharmD, BCPS-AQID, said that implementation of a successful antimicrobial stewardship program requires support from hospital administrators and the developers and users of the stewardship policies. “If you’re going to have initiatives [and] optimize antibiotic use, you have to ultimately have support from the C-suite,” said Dr. Pogue.

Debra Goff, PharmD, said that she uses “the 5 Ds” to ensure the responsible use of antimicrobials to offset antibiotic resistance and decrease adverse events: making the correct diagnosis; selecting the correct drug, dose, and duration; and having the potential for de-escalation of therapy.

“If all you look at is antibiotic use, you’re missing the picture,” she said. “You have to have more than just the physician who might be labeled as in charge of stewardship. You need all physicians engaged.”

However, Dr. Goff pointed out that expecting all physicians to know the details of first-line therapy for various types of infections is impractical. “I don’t expect a surgeon to know what a carbapenem-resistant Enterobacteriaceae is,” she said. “I tell them, “That’s not your job. What I need you engaged with is to engage with us and follow the guidelines. We’ll give you the rationale. We’ll give you the guidance. We teach them how to use the drugs responsibly, [and] then when you get the call for an antibiotic on the protected list, all the newer agents, it’s a 2-second phone call.”

Technology and Data

Sandy J. Estrada-Lopez, PharmD, said that institutions are figuring out ways to use electronic health records (EHRs) to identify which patients get infected, the type of pathogen they are infected with, and the best drug match for the pathogen. To obtain this information, some institutions use add-on systems, such as TheraDoc or MedMined, whereas the makers of the Epic system—used at her institution (Lee Memorial Health System) and others—are developing more robust modules for infection prevention and antimicrobial stewardship. Dr. Pogue also said that the IT department at his institution (Sinai-Grace Hospital of Detroit Medical Center) implemented an alert in the EHR if a physician attempts to order an antibiotic when a patient has recently had an organism resistant to that antibiotic.

Dr. Goff added that involvement of the hospital IT department is important for generating meaningful reports that can be used for justifying the use of expensive antibiotics for select patients.
or identifying patients at high risk for *Clostridium difficile* infection. She noted that for the latter situation, the IT department could create an alert when a proton pump inhibitor (PPI) is prescribed to a patient already on antibiotics or when 3 antibiotics are ordered for a patient already taking a PPI. “There are ways you strategize to figure out who is the highest-risk patient to get *C. difficile* in your hospital instead of me trying to look at every antibiotic [and] every PPI,” she said. “That’s an extremely time-consuming way to approach it.”

Dr. Pogue also emphasized that providing the IT department with data demonstrating the effectiveness of the technology shows them the value of their input, which encourages them to participate in the development of antibiotic stewardship. “You’ll see reporting come up as one of these core elements of stewardship,” he said. “It’s getting that data back. We asked for a lot at my institution of our pharmacists and physicians when we revamped vancomycin dosing. They had to do a whole lot of extra steps because we thought it would be safer, and it was safer. I go to the pharmacy meeting and I say, ‘Look at these numbers.’ That gets buy-in [from the C-suite] and reinforces the importance of what you’re trying to do, which is ultimately improve patient outcomes.”

However, Andrew Shorr, MD, cautioned that stewardship is a relatively new endeavor and the effectiveness of potential protocols need to be assessed using clinical trials that compare 2 approaches. “When we start having randomized controlled trial data and we really are focused on a tool for a better kind of approach, we can actually start to apply that and say [that] the no up-front strategy is a fail, and this is the cost. But an audited feedback approach clearly offers benefits, and it’s easier to change physician behavior because that’s what this is all about with evidence.”

GOALS AND CHALLENGES

The panelists agreed that the responsible use of antibiotics to optimize care of the patient is the primary goal of an effective stewardship program, and Dr. Pogue added that activities of the stewardship program should also work to minimize the unintended consequences of toxicity, antibiotic resistance, and *C. difficile* infection.

Additionally, educating other physicians, such as surgeons and oncologists, on the consequences of prophylactic antibiotics is important, according to Dr. Goff. “The prescribing of antibiotics is often just in case they might have an infection because they’re perceived as benign drugs with minimal risk,” she said. “Now the risk is much greater than that perceived benefit, and that’s what we’re trying to change. Stewardship has to convey that.”

Dr. Estrada-Lopez agreed that the education of other physicians on the negative consequences of unnecessary antibiotic prescribing has been relatively poor and that the lack of education is particularly evident in the outpatient setting where antibiotic use is often driven by patient request.

“Many patients want antibiotics just in case,” she said. “We’ve done a lot with education [of physicians] on ‘Use this, this is the spectrum,’ but not as much on the ‘nothing at all’ because they don’t really have an infection or really think about the total risk-benefit.”

CONCLUDING REMARKS

According to the panelists, the best, and most obvious, way to avoid antibiotic resistance is to prevent infections that require treatment with an antibiotic. Dr. Shorr added that widespread promotion of up-to-date vaccinations and implementation of everyday measures in the intensive care unit to prevent infection when possible, such as elevating the bed, using orogastric instead of nasogastric tubes, and decreasing sedation, can help prevent development of resistant bacterial infections.

Hand washing is also important for preventing infection, and Dr. Shorr noted that the compliance rates are appallingly low. He stated that hand hygiene compliance among health care providers may be improved by placing hidden cameras and ensuring the hand sanitizer dispensers are refilled regularly throughout the hospital.

The panelists concluded that treating multidrug-resistant infections and promoting antimicrobial stewardship requires collaborative efforts among health care providers, patients, and hospital administrators. Dr. Estrada-Lopez said, “Working together, educating each other, and understanding how the role that we play can make a difference for patient care will lead us to the next steps in the future of decreasing antimicrobial resistance.”

Dr. Pogue added that getting patients on the correct antibiotic is a key component of stewardship and involves taking patient-specific information and local epidemiology information and using new antimicrobials judiciously. “Think what’s best for your patient as well as the hospital and get your patients on the best therapy,” he said.

Dr. Shorr concluded that collaborating with policy makers, legislators, and pharmaceutical developers will be important to increase recognition of antibiotics as a public resource that requires public stewardship. “We really need to be appealing to our policy makers and our legislators to realign incentives so that quality payments reflect quality behavior as opposed to punishments for the hospital [and] that pharmaceutical developers have legitimate reasons to risk the capital to go in and develop antibiotics that don’t pay the way chronic cancer therapies do,” he said. “All of these things need to change at a national level if we’re going to have the tools we need.”

“Outsmarting Resistant Infections”

**Moderator**

Peter L. Salgo, MD

Professor of Medicine and Anesthesiology, Columbia University College of Physicians and Surgeons

Associate Director of Surgical Intensive Care at NewYork-Presbyterian Hospital

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**Panelists**

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Clinical Associate Professor and Infectious Disease Specialist, The Ohio State University Wexner Medical Center

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ContagionLive.com/link/857
2018 National STD Prevention Conference

CDC Reports Sharp, Continuous Increase in STDs Over Past 4 Years
BY KRISTI ROSA

(continued from cover) who are gay or bisexual or men who have sex with men, according to the presentation.

Furthermore, more than 1.7 million cases of chlamydia were diagnosed in 2017, according to the data. The disease remained the most common STD reported to the CDC, and a little less than half of the reported cases (45%) were among women aged 15 to 24.

A 67% overall increase in the number of gonorrhea diagnoses was reported, jumping from 333,004 cases to 555,608 cases, with the number of these diagnoses increasing 2-fold in men since 2013. However, the rapid increase in cases reported in women is even more concerning, according to the CDC, as numbers have risen for the third consecutive year.

Although the CDC recommends 2 antimicrobials to treat uncomplicated gonorrhea—250 mg of ceftriaxone intramuscular and 1 g of oral azithromycin—results from a recent report showed that only 81% of patients infected with uncomplicated gonorrhea are receiving the recommended regimen.7 Treatment adherence is imperative, especially as the number of cases of drug-resistant gonorrhea also continues to grow.

"Our first-line drugs—combination cephalosporins and azithromycin—are still effective for gonorrhea, but we’re seeing an emerging case reports of resistance to these drugs, which is of huge concern,” Christine Johnston, MD, MPH, an associate professor in the Division of Allergy and Infectious Diseases, University of Washington, Seattle, and medical director of the University of Washington STD Prevention Training Center, part of the CDC-funded National Network of STD/HIV Prevention Training Centers, said in a recent interview with Contagion®.

She added that although she has not seen resistance to the combination therapy recommended by the CDC for gonorrhea in her practice, it could still occur. “The main concern is that we are marching through classes of antibiotics for treatment,” she said. “Several drugs have been available, but gonorrhea has rapidly acquired resistance with use of these drugs.”

Although emerging resistance to ceftriaxone has not been observed since the dual therapy recommendation was implemented, the new analysis reports that emerging resistance to azithromycin has increased from 1% in 2013 to 4% in 2017 in laboratory testing.

“We expect gonorrhea will eventually wear down our last highly effective antibiotic, and additional treatment options are urgently needed,” Gail Bolan, MD, director of the CDC’s Division of STD Prevention, said in a statement.1

“We can’t let our defenses down—we must continue reinforcing efforts to rapidly detect and prevent resistance as long as possible.” To reverse these trends, the CDC has issued a call to action for health care providers to make screening for STDs and providing timely treatment a standard part of medical care.

The data was presented at the CDC’s 2018 National STD Prevention Conference, held in Washington, DC, from August 27 to 31, 2018. ▲

References available at ContagionLive.com.

Missed Opportunities for PrEP Prescribing in High-Risk Populations
BY MICHAELA FLEMING

(continued from cover) prescribing practices,” Alyson Decker, MS, MPH, NP, a clinical prevention consultant for the San Francisco City Clinic in California, told Contagion®.

“In addition, the survey helps to inform and direct the conversation with providers and measure program outcomes.”

The results of the survey were presented at the US Centers for Disease Control and Prevention’s 2018 National STD Prevention Conference, held in Washington, DC, from August 27 to 31, 2018.

As part of the investigative process, from October 2016 to October 2017, a nurse practitioner visited various practices to provide tailored training on the benefits and use of PrEP to providers with patients who included MSM and transgender women. During the session, a survey was conducted. The paper-based, self-report survey was administered to providers by the nurse practitioner.

The investigators collected 252 surveys from 47 clinician practices. The majority of surveyed participants (82%) were primary care providers, while 23% were HIV care providers. Only 48% of the providers had ever prescribed PrEP. Furthermore, approximately 60% of the participants reported that they do not routinely conduct an annual sexual history of their patients.

Of the 204 providers who reported working with MSM and/or transgender patients, 78 (38%) reported they do not routinely inquire about receptive anal intercourse with their patients. Additionally, 70 providers (33%) reported that they did not screen patients for rectal sexually transmitted diseases, such as gonorrhea and chlamydia.

Factors associated with prescribing PrEP included regularly conducting a sexual history versus not obtaining the history (59% vs 41%; P <.05), determining receipt of anal intercourse versus not (67% vs 33%; P <.05), and screening patients for rectal sexually transmitted diseases versus not screening (69% vs 31%; P <.05).

The findings exposed gaps in missed opportunities for sexually transmitted disease screening and PrEP prescribing. “When providers do not routinely talk with patients about their sexual health, then they are unable to identify those who might benefit from these important prevention strategies,” stressed Ms. Decker.

As a result of these findings, the San Francisco Department of Public Health is launching a follow-up sexual health campaign to increase the frequency of providers’ discussions of sexual health and tests for sexually transmitted diseases in their clinical practice.

Ms. Decker, who has been involved in the follow-up campaign, provided insight into how similar programs can be created to advocate for sexually transmitted disease screening and PrEP use.

“My advice to other health departments would be to have concise, behavior-based messaging,” she said. “[You need to] clearly state the action that you are hoping to change instead of just providing facts and figures. For instance, take a comprehensive sexual history that includes the gender of sexual partners and anatomic sites of sexual exposure during the past year. Limit the campaign to 2 to 4 messages, and tailor your materials and detailing around these messages.” ▲

References available at ContagionLive.com.
Using a “Kick-and-Kill” Approach to Cure HIV

BY KRISTI ROSA

(continued from cover)

different therapy combinations to fight dormant HIV reservoirs. It also demonstrates the importance of looking outside current therapeutic approaches in the quest for a cure, the author added.

Led by investigators from Imperial College London, the University of Oxford, the Medical Research Council Clinical Trials Unit at University College London, and the University of Cambridge, the randomized phase 2 trial assessed the kick-and-kill approach in 60 men who had recently been given an HIV diagnosis and were virally suppressed on ART. The trial ran from 2015 to 2018 in London and Brighton, England.

Because individuals on ART can achieve viral suppression and have undetectable levels of HIV in their blood if they adhere to their therapy regimen, they are also rendered sexually noninfectious. Viral suppression does not equate to a cure; however, and if an individual stops ART, dormant HIV hiding in reservoirs can reanimate and cause active infection again. As such, investigators hypothesize that a cure for HIV may lie in killing the virus hiding out in these reservoirs. "For those who have access to it, ART brings amazing success in managing HIV, but people have to take it for most of their lives," chief investigator Sarah Fidler, PhD, MBBS, FRCP, a professor at Imperial College London, said in a statement. "We have to think about other, sustainable alternatives, and a cure or at least some form of remission is a key goal."

This is where the kick-and-kill strategy comes in.

For the RIVER trial, investigators used 2 therapies in addition to standard ART: vorinostat (Zolinza, Merck), typically used for managing cancer, to “wake up” reservoir cells (CD4 T cells) by forcing HIV out of its hiding place to face the immune system, and a combination of 2 vaccines—ChAdV63.HIVconsv and MVA.HIVconsv—to help the immune system not only recognize HIV but also eliminate it.

The goal of the trial was to significantly decrease viral levels in the CD4 T cells of individuals receiving the kick-and-kill treatment. However, when the results first came out, in April 2018, the investigators found that those who were given this approach in addition to ART still had levels of infected CD4 T cells comparable to those in individuals who received standard ART.

"In the RIVER study, we found that all the separate parts of the kick-and-kill approach worked as expected and were safe," Dr. Fidler explained. "The vaccine worked on the immune system, the kick drug behaved as we expected it to, and the ART worked in suppressing viral load in the body, but the study has shown that this particular set of treatments together didn’t add up to a potential cure for HIV, based on what we’ve seen so far."

Because of their findings, the investigators were unable to recommend that participants receive the kick-and-kill drugs in addition to ART; furthermore, the team did not find evidence to support safely stopping ART for any of the study participants.

“We need to think about why we didn’t see an effect,” coprincipal investigator and scientific lead of the study John Frater, a professor at the University of Oxford, stressed. "The important thing to realize is that despite these disappointing results, it does not mean that the basis of the approach is wrong.” He added that the issue could have been in the combination of the drugs used and that vorinostat may not have been potent enough to wake up as much of the virus as needed for the immune system to recognize it.

Administering more boosts of the vaccine with a different “kick” drug may be explored in further research, according to the investigators. In addition, evaluating the next generation of the vaccines used in the study that are now being assessed in other trials could also be worth further exploration.

The society’s meeting was held July 23 to 27, 2018, in Amsterdam, the Netherlands.

IAS–USA Releases 2018 Guidelines for HIV Treatment and Prevention

BY EINAV KEET

(continued from cover)

some revisions include:

- Initial regimen updates that focus primarily on unboosted integrase strand transfer inhibitor regimens.
- Encouragement of rapid initiation of ART, including same-day initiation, if feasible.
- Recommendation against the routine use of mycobacterium avium complex prophylaxis for those with advanced disease on effective ART.
- Recommendation for the discontinuation of routine CD4 count lab testing once a patient has sustained undetectable HIV RNA levels for a year and has a CD4 count above 250 cells/μL.
- Recommendation for an alternative for preexposure prophylaxis (PrEP) for those who are not infected with HIV but remain at risk for infection, to now include an episode-based approach in which individuals can take preventive ART pills prior to exposure and a follow-up pill once daily for 2 days post exposure.

“We know that antiretroviral therapy is the cornerstone of prevention and management of HIV infection,” said lead author Michael Saag, MD, director of the University of Alabama at Birmingham’s Center for AIDS Research, in a statement. “[However,] it’s critical to continually evaluate new data and treatments for initiating therapy, monitoring individuals starting therapy, changing regimens and preventing HIV infection for those at risk, [and] reaffirming the standard of providing the utmost treatment and care possible.”

Care for HIV continues to evolve, study coauthor Paul Volberding, MD, professor at the University of California, San Francisco, added. As such, clinicians and patients need to apply the latest knowledge to keep pace with the ways in which it has changed. The guidelines, according to Dr. Volberding, have been developed to provide a concise and current set of recommendations that capture the direction HIV care is taking.

In an accompanying editorial, author James Riddell IV, MD, professor of infectious diseases and internal medicine at the University of Michigan, noted that despite the availability of highly potent, single-tablet ART and a sophisticated medical infrastructure, too many individuals infected with HIV still are not receiving treatment and achieving viral suppression.

Guidelines serve an important purpose, however, they “serve only as a starting point, as evidenced by the fact that implementation has proved to be much more challenging,” wrote Dr. Riddell. “It is now clear that to effectively address the HIV epidemic, a multipronged approach is needed that includes new HIV prevention strategies (HIV PrEP, education regarding condom use), expanded HIV testing, rapid and immediate linkage to care when possible, viral suppression for persons who are HIV infected, and strategies to enhance adherence to therapy and retention in care.”

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Patients With Diabetes Soon to Have New Option for ABSSSIs

BY CONTAGION® EDITORIAL STAFF

(continued from cover)

Patients with diabetes treated with iclaprim experienced numerically fewer adverse events than patients treated with vancomycin.

Iclaprim could potentially solve these issues,” continued Dr. Huang, “because it is bactericidal and may work among immunocompromised populations, including patients with diabetes, as well as patients with peripheral vascular disease who have micro- and macroangiopathies because it is a small molecule, activity is not affected among patients with gastrointestinal and renal impairment because it is metabolized by CYP3A4 and 2D19 liver enzymes, does not cause nephrotoxicity, and has limited to no clinically significant drug–drug interactions that would require dose adjustment of iclaprim.”

Iclaprim is a novel investigational antibiotic that is effective against gram-positive multidrug-resistant bacteria, such as methicillin-resistant Staphylococcus aureus, with activity against some gram-negative bacteria, including Haemophilus influenzae and Moraxella catarrhalis. Its unique mechanism of action, which involves interfering with dihydrofolate reductase has the drug manufacturer, Motif Bio, positioning it as a targeted gram-positive antibiotic. (Only 1 other drug, trimethoprim, has the same target.) The results of previous studies, such as REVIVE-1 and REVIVE-2, previously reported on in Contagion®, have shown that iclaprim is noninferior to vancomycin for the treatment of ABSSSIs.

For this post hoc study, investigators analyzed data from the REVIVE studies to determine the safety of iclaprim versus vancomycin for the treatment of ABSSI among patients with diabetes. After first identifying those patients in the study with diabetes, the investigators evaluated them “for safety on the basis of medical history and physical examinations, routine electrocardiography, laboratory tests, urinalysis and reports of clinical AEs,” according to the study abstract. Investigators were blinded to each treatment assignment; however, they categorized AE severity and relationship to the study drug. The Cockcroft-Gault formula was used to determine baseline renal impairment.

The study results revealed that 11% (n = 127) of the patients in the intention-to-treat (ITT) arm of the REVIVE studies had diabetes, and 37.8% had some type of renal impairment. A total of 71 patients were treated with vancomycin, while 56 were treated with iclaprim. Among the patients in the pooled ITT population, renal impairment was common. Twenty-two (39.2%) of the 56 patients with diabetes in the iclaprim group had mild, moderate, or severe renal impairment, while 26 (36.6%) of the 71 patients in the vancomycin group had such impairment.

AEs were found to be “numerically lower in the iclaprim group compared with the vancomycin group,” according to the study abstract. A total of 3 patients in the vancomycin arm developed acute kidney injury and increased creatine levels, while none of the patients in the iclaprim arm developed these renal AEs in the REVIVE studies. Two (3.6%) of the patients in the iclaprim arm discontinued the study because of an AE versus 7 (10.0%) patients in the vancomycin arm.

According to the investigators, diabetic patients treated with iclaprim experienced numerically fewer AEs than patients treated with vancomycin (48.2% vs 52.9%). Patients with diabetes and renal impairment may be more vulnerable to vancomycin-related AEs, and therefore, the investigators stated that further evaluation is warranted, particularly considering the frequent occurrence of diabetes among hospitalized patients with ABSSSIs and the broad use of vancomycin in hospital settings.

“Motif continues to perform post hoc analyses from the REVIVE trials that include clinical efficacy and safety among subpopulations, microbiological responses among different pathogens identified in the trials, and pharmacokinetic and pharmacodynamic analyses among various efficacy and safety parameters and different subpopulations,” concluded Dr. Huang. “In addition, iclaprim has been shown to suppress bacterial toxin suppression in in vitro studies, which may impact outcomes especially among patients with necrotizing infections [skin and pneumonia].”

Motif Bio submitted a new drug application for iclaprim in August 2018. It was accepted and also granted priority review for the treatment of ABSSSIs, and the FDA’s decision date under the Prescription Drug User Fee Act is slated for February 13, 2019.

The study was presented at the European Society of Clinical Microbiology and Infectious Diseases/American Society for Microbiology (ASM) Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance, which took place in Lisbon, Portugal, from September 4 to 7, 2018. ▲

References available at ContagionLive.com.
Iclaprim Shows Consistent Activity Against β-Hemolytic Streptococci

BY KRISTI ROSA

(continued from cover)

we can’t say conclusively—it will be very difficult for resistance to occur because of its 2 mechanisms,” William O’ Riordan, MD, FACP, chief medical officer of eStudySite, told Contagion® in a past interview. “I think it is unique feature of this antibiotic. It interferes with DHFR, which is intimately involved with the bacterial cell and the cell integrity and does away with the cell itself.”

For the study, investigators tested iclaprim and other antibiotics against isolates of drug-susceptible and -resistant β-hemolytic streptococci collected from patients with skin and skin structure infections worldwide from 2012 to 2016.

Antibacterial susceptibility testing was performed by broth microdilution on a total of 458 nonduplicate, nonconsecutive isolates—257 were Streptococcus pyogenes, and 201 were Streptococcus agalactiae. The isolates were collected from several regions across the globe, including Europe (n = 205), North America (n = 204), Latin America (n = 26), and Asia Pacific (n = 23).

The investigators used Clinical and Laboratory Standards Institute breakpoints to interpret minimum inhibitory concentrations (MICs): erythromycin (susceptible [S] ≤0.25, resistant [R] ≥1.0 µg/mL), azithromycin (S ≤0.5, R ≥2.0 µg/mL), and tetracycline (S ≤2.0, R ≥8.0 µg/mL).

Iclaprim demonstrated consistent and potent activity against S pyogenes in isolates that were susceptible or resistant to erythromycin and azithromycin. Furthermore, the investigators noted that MIC50 and MIC90 (µg/mL) values were higher for iclaprim in isolates that were tetracycline-resistant S pyogenes compared with tetracycline-susceptible isolates.

Iclaprim also proved to have consistent and potent activity against S agalactiae. The investigators reported that MIC50 and MIC90 (µg/mL) values against drug-susceptible isolates were either identical or within 2-fold of those observed against erythromycin-, azithromycin-, and tetracycline-resistant isolates.

As such, the investigators concluded that iclaprim demonstrated activity against a worldwide collection of drug-susceptible and -resistant β-hemolytic streptococci collected from patients with skin and skin structure infections.

With bacteria becoming increasingly resistant to available antibiotics, the need for more treatments with a low propensity for resistance development is critical.

“Continued surveillance is warranted to monitor the activity of iclaprim against β-hemolytic streptococci,” the investigators wrote, “as well as to detect any potential emergence of resistance.”

The US Food and Drug Administration accepted a new drug application and granted priority review for iclaprim in August for the treatment of acute bacterial skin and skin structure infections.

The approval was based on promising results yielded from 2 phase 3 trials, REVIVE-1 and REVIVE-2, which established the safety and efficacy of the drug compared with vancomycin, the standard of care.

The study was presented at the European Society of Clinical Microbiology and Infectious Diseases/American Society for Microbiology (ASM) Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance, which took place in Lisbon, Portugal, from September 4 to 7, 2018. ▲

References available at ContagionLive.com.
Salt, Ticks, and Lyme: A Case of Lyme Neuroborreliosis Presenting as SIADH

This case report is the fourth documented case of Lyme-induced SIADH.

BY NIHAAL KARNIK, MD; JAMES ROSSI, MD; ROHAN PARIKH, MD; AND RAVINDRA SANGITHA, MD

HISTORY OF PRESENT ILLNESS

A 79-year-old man with a medical history of coronary artery disease and hypertension presented to the emergency department (ED) with acute onset of ataxia and double vision in June 2018. Two days prior to his admission, he was seen at an outside ED for complaints of a headache. At the outside facility, he was found to have a blood pressure of 210/105 mm Hg, which was reduced with oral antihypertensives. Imaging at that hospital did not demonstrate any acute hemorrhage, and he was discharged with instructions to follow up with his primary care provider.

On the morning of the current admission, he awoke feeling ataxic and weak and had diplopia. He attempted to ambulate and subsequently fell while getting out of bed. He denied syncope or any postictal symptoms during this episode. The history was obtained from his daughter, who was at his bedside. The patient was unable to give a history secondary to his condition.

MEDICAL HISTORY

Coronary artery disease, with a known drug-eluting stent placed in 2009; hypertension; hyperlipidemia; and gout.

MEDICATIONS

Norvasc 10 mg by mouth daily; losartan 100 mg by mouth daily; metoprolol 50 XL daily; atorvastatin 40 mg by mouth every night at bedtime; allopurinol 300 mg by mouth daily; aspirin 81 mg by mouth daily.

EPIDEMIOLOGICAL HISTORY

The patient was sexually active with his wife of 50 years, a nonsmoker, and a nondrinker and denied any illicit drug use. His family denied any recent travel outside the Pennsylvania area over the 6 months prior to presentation. He and his family denied any recent illness or sick contacts. He also did not own any pets, and his family did not recall any obvious pet exposures.

PHYSICAL EXAMINATION

The patient’s vital signs were within normal limits. On physical examination, he was lethargic and unable to respond coherently and appeared very fatigued. His mucous membranes were moist, and he did not have any signs of volume overload (eg, jugular venous distention, edema). His pupils were equal, round, and reactive to light, but he could not abduct his eyes. His cardiovascular assessment did not reveal any murmurs or arrhythmias, and his thoracic examination was unremarkable. His neurological...
examination was remarkable for 2 out of 5 strength in his upper and lower extremities, bilaterally.

RELEVANT LABORATORY DATA
Given his concerning physical examination, laboratory work was ordered to discern the etiology of his condition. Complete blood count was unremarkable; however, serum sodium was found to be 125 mEq/L (normal: 135-145 mEq/L). A chart review revealed a serum sodium level of 138 mEq/L 2 days prior to admission.

Further laboratory evaluation of the patient’s hyponatremia demonstrated serum osmolality of 269 mOsm/kg (normal: 275-295 mOsm/kg), urine osmolality of 688 mOsm/kg, urine sodium of 87 mmol/L, and uric acid of 3 mg/dL.

CLINICAL COURSE
The patient presented to the hospital with concerning physical examination and metabolic derangements. Initially, the work-up and management concerned his hyponatremia. On presentation, his hyponatremia was classified as hypotonic and euolemic. Given his high urine osmolality and high sodium, his hyponatremia appeared to be related to syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The patient was placed on fluid restriction for initial management of SIADH and did not show much neurological improvement or correction of his hyponatremia. Because fluid restriction usually corrects underlying hyponatremia related to SIADH, additional etiologies were sought. Thyroid and adrenal studies were checked, as these functions are known to also mimic or confound a diagnosis of SIADH, but results were within normal limits.

Given that the etiology of the patient’s SIADH remained a mystery, radiological surveillance was undertaken to search for any possible lesions or malignancies. A chest x-ray was concerning for a possible lesion in the thoracic cavity, which led to further evaluation via bronchoscopy. It was thought that the patient may have had neuroendocrine sequelae of SIADH related to a possible thoracic malignancy. However, the results of the bronchoscopy proved to be fruitless and were simply demonstrative of a mucous plug, which had no clinical significance.

The patient was not improving, so a reassessment of the history of the present illness was repeated with his family members. A careful and in-depth history revealed that 2 months prior to presentation, the patient had been hiking in the woods with his grandchildren and could have been bitten by a tick. This led to subsequent testing for Lyme disease, which was confirmed via a Western blot analysis.

Once the appropriate diagnosis of Lyme disease was made, intravenous ceftriaxone therapy was initiated. There was a rapid improvement in the patient’s metabolic panel and his neurological status (Figure). On the day of discharge, the patient was more lucid, was answering questions appropriately, and had full strength in his upper and lower extremities. He finished a 4-week course of ceftriaxone with resolution of his ataxia and diplopia.

DIAGNOSTIC PROCEDURES AND RESULTS
* * * • Borrelia burgdorferi* enzyme-linked immunoabsorbent assay with a reflexive Western blot demonstrating 6 confirmatory IgG bands: 18 kDa, 28 kDa, 30 kDa, 39 kDa (BmpA), 45 kDa, and 66 kDa.

DISCUSSION
Hyponatremia is the most common electrolyte imbalance seen in clinical practice. In patients older than 65 years, SIADH was the main culprit in over half of all cases of hyponatremia. The most common etiologies of SIADH are malignancy, medications, and central nervous system (CNS) disorders. CNS infections are a rare but known cause of SIADH and include bacterial and enteroviral meningitis, tuberculosis, herpes simplex, St. Louis encephalitis, and La Crosse encephalitis. Management of SIADH involves treating the underlying etiology; however, management becomes more difficult when the cause of the SIADH is not identified and significantly affects the patient.

This patient initially presented with vague neurological symptoms and hyponatremia, identified as SIADH. Multiple imaging modalities and invasive tests, including bronchoscopy, were performed, but a cause for the SIADH remained unknown. Eventually, a thorough discussion with the family revealed that the patient went hiking in the woods 2 months prior to presentation. Lyme disease was positive after testing but was not identified as an etiology for the SIADH. It was not until antibiotic treatment was initiated that the patient’s hyponatremia and symptoms resolved.

Lyme-induced SIADH is a rare phenomenon, and only 3 case reports were found in the literature. A review of the cases revealed almost identical presenting symptoms and hospital course to the patient’s. In the case reports, the patients were eventually tested for Lyme disease, and after appropriate antibiotic treatment was initiated, complete resolution of all symptoms and hyponatremia occurred.

This case identifies 3 major problems that affected the patient: a prolonged hospital course, a significant financial burden, and a delay in care. Our patient underwent multiple imaging studies, including invasive testing, but a clear cause for the SIADH could not be determined. In addition to having to wait for the diagnosis of Lyme disease, the patient was exposed to a prolonged hospital course and incurred unnecessary medical costs. A more thorough history and education about the lesser-known consequences of Lyme could have led to earlier diagnosis.

In addition, further research is needed regarding the pathophysiology and sequelae effects of Lyme-induced SIADH. Given that the hypothalamus secretes antidiuretic hormone, it is clear that CNS involvement of Lyme disease may be associated with endocrinopathies. Understanding this mechanism may broaden the understanding of not just Lyme disease but also the interplay between tick-borne illnesses and undiagnosed or perplexing endocrinopathies.

SIADH is a common disorder that can be treated only by identifying the correct etiology. When practitioners are unable to determine the root cause, patients undergo a prolonged hospital course, incur significant medical costs, and experience a delay in care. Resolution of the patient’s SIADH ultimately occurred after discovery and treatment of Lyme disease via the least expensive modality: a more thorough history. This case report is the fourth documented case of Lyme-induced SIADH. All cases had similar hospital courses, including incidental diagnosis of Lyme and complete resolution of symptoms when antibiotics were administered. This case report is another piece of evidence to support this medical phenomenon and stresses the importance to the medical community of including Lyme disease as a differential for SIADH.

References available at ContagionLive.com.
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